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Editorial

Totally drug-resistant tuberculosis (TDR-TB): A debate on global health communities

To date, totally drug-resistant tuberculosis (TDR-TB) has been documented in four countries: Italy, Iran, India and South Africa [1–4]. TDR-TB bacilli, which are sometimes referred to as extremely drug resistant TB (XXDR-TB), showed in vitro resistance to all first- and second-line TB drugs tested [1,2]. The term TDR-TB was proposed for multi-drug resistant TB (MDR-TB) patients that remained smear and culture positive after 18 months of median treatment despite second-line drug therapy [2]. In these patients, treatment with Co-amoxiclav (625 mg/8 h) or Clarithromycin (1000 mg/day^{-1}) along with a high dose of isoniazid (15 mg/kg^{-1}) had no improvement and the majority of cases had expired within the next two years of follow-up [2,5]. This means that TDR-TB is even worse than MDR and extensively drug-resistant TB (XDR-TB). The crisis may become more complicated in countries where huge numbers of adults live with HIV. Fortunately, the emergence of such deadly bacilli alerts the TB experts worldwide [6,7]. But the World Health Organization (WHO) declined to officially recognize TDR-TB on the grounds that "lab tests done to confirm resistance to second-line anti-TB drugs are unreliable and often not reproducible [8]."

With availability of TDR-TB isolates in the Iranian National Reference TB Laboratory (NRL), the investigation at the cellular and the molecular levels was started. The culture suspension of TDR-TB bacilli were isolated and observed under scanning, electron or atomic force microscopy. The results showed morphological variation in shape, size, cell-division and cell-wall content of TDR-TB bacilli [9–12]. Additionally, the pili or tube-like structure (10–15%) was found on their culture isolates [11,13]. Even careful observation of positive smear or culture specimen under light microscopy could reveal the round or oval shape TDR-TB bacilli (Figs. 1–3). All these adaptations raise new debate on Koch bacilli. For example, the rate of transmission and the time that round TDR-TB bacilli can remain suspended in the air is not known. We even do not know how the TB laboratory and clinical personals should be protected. In addition, what will be the proposed policy of isolating patients that carry such deadly bacilli? On the other hand, the fate of round TDR-TB bacilli in the host and how it provokes the immune responses has to be investigated. These challenges underline the urgent need of discussing and reviewing the TDR-TB bacilli as "a new serve form of tuberculosis."

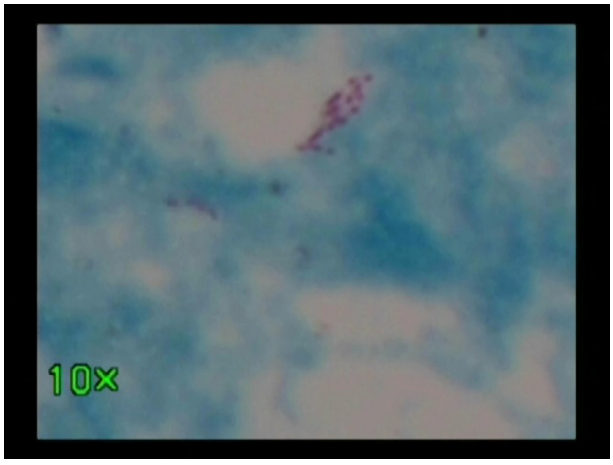

Fig. 1 – Round shaped TDR-TB bacilli; *Ziehl–Neelsen* staining of digested sputum sample.

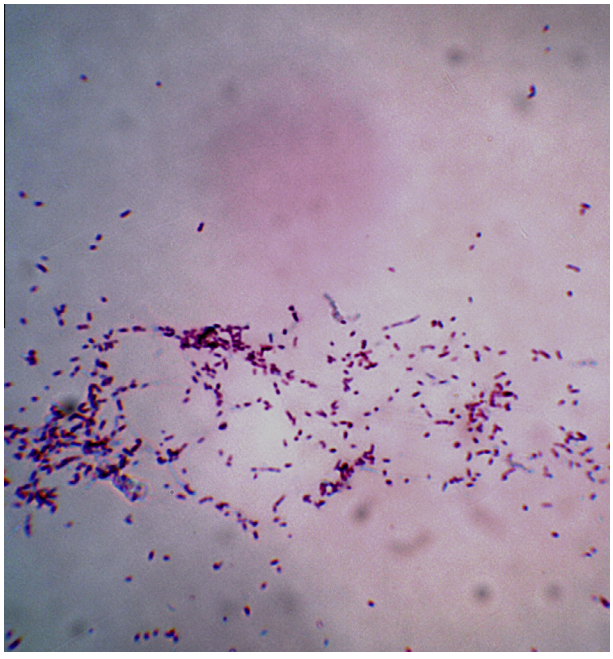

Fig. 2 – TDR-TB bacilli isolated from AFB culture-positive samples; *Ziehl–Neelsen* staining.

Fig. 3 – Modified silver staining method; variable shape of TDR-TB bacilli under light microscopy. The percentage of round or oval shape cells are varied from 15% to 30% in different patients.

Recently, there was a ray of hope when SIRTUROTM (Bedaquiline) by Johnson & Johnson Company had FDA approval [14]. Bedaquiline is the first medication exclusively manufactured for MDR-TB patients [15]. The drug proved to be effective in the first and second clinical trials, but the overall benefit remains unproven, especially when the manufacturer reported an increased risk of death (11%) in comparison with the placebo treatment group [14]. Overall, even if Bedaquiline proves to be effective in MDR patients, it may take several years to reach the developing countries. Therefore, as far as there is no cure for TDR-TB patients, it is not exaggerating to say that the world is in danger of an untreatable drug-resistant TB strain [5].

REFERENCES

[1] G.B. Migliori, G. De Iaco, G. Besozzi, R. Centis, D.M. Cirillo, First tuberculosis cases in Italy resistant to all tested drugs, Euro Surveill. 12 (5) (2007) E070517.1.
[2] A.A. Velayati, M.R. Masjedi, P. Farnia, P. Tabarsi, J. Ghanavi, A.H. Ziazarifi, et al, Emergence of new forms of totally drug-resistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug-resistant strains in Iran, Chest 136 (2) (2009) 420–425.
[3] Z.F. Udwadia, R.A. Amale, K.K. Ajbani, C. Rodriguez, Totally drug-resistant tuberculosis in India, Clin. Infect. Dis. 54 (4) (2012) 579–581.
[4] M. Kolpper, R.M. Warren, C. Hayes, N.C.G.V. Pittius, E.M. Streicher, B. Müller, et al, Emergence and spread of extensively and totally drug-resistant tuberculosis, South Africa, Emerg. Infect. Dis. 19 (2) (2013) 449–455.
[5] A.A. Velayati, P. Farnia, M.R. Masjedi, The totally drug resistant tuberculosis (TDR-TB); fact sheet, Int. J. Clin. Exp. Med. 6 (4) (2013) 307–309.
[6] J.A. Caminero, Treatment of tuberculosis according to the different pattern of resistance, Med. Clin. 134 (4) (2010) 173–181.
[7] V. Vincent, L. Rigouts, E. Nduwamahoro, B. Holmes, J. Cunningham, M. Guillerm, et al, The TDR tuberculosis strain bank: a resource for basic science, tool development and diagnostic services, Int. J. Tuberc. Lung Dis. 16 (1) (2012) 24–31.
[8] World Health Organization. Totally drug resistant tuberculosis: a WHO consultation on the diagnostic definition and treatment options. WHO, Geneva, 2012. <www.who.int/tb/challenges/xdr>.
[9] A.A. Velayati, P. Farnia, T.A. Ibrahim, R.Z. Haroun, H.O. Kuan, J. Ghanavi, et al, Differences in cell wall thickness between resistant and nonresistant strains of *Mycobacterium tuberculosis*: using transmission electron microscopy, Chemotherapy 55 (5) (2009) 303–307.
[10] A.A. Velayati, P. Farnia, M.R. Masjedi, T.A. Ibrahim, P. Tabarsi, R.Z. Haroun, et al, Totally drug-resistant tuberculosis strains: evidence of adaptation at the cellular level, Eur. Respir. J. 34 (5) (2009) 1202–1203.
[11] A.A. Velayati, P. Farnia, M.A. Merza, G.K. Zhavnerko, P. Tabarsi, et al, New insight into extremely drug-resistant tuberculosis: using atomic force microscopy, Eur. Respir. J. 36 (6) (2010) 1490–1493.
[12] P. Farnia, R.M. Mohammad, M.A. Merza, P. Tabarsi, G.K. Zhavnerko, T.A. Ibrahim, et al, Growth and cell-division in extensive (XDR) and extremely drug resistant (XXDR) tuberculosis strains: transmission and atomic force observation, Int. J. Clin. Exp. Med. 3 (4) (2010) 308–314.
[13] A.A. Velayati, P. Farnia, M.R. Masjedi, Pili in totally drug resistant *Mycobacterium tuberculosis* (TDR-TB), Int. J. Mycobacteriol. 1 (3) (2012) 57–58.
[14] M. Mirsaeidi, After 40 years, new medicine for combating TB, Int. J. Mycobacteriol. 2 (1) (2013) 1–2.
[15] <http://www.fda.gov//newsEvents/Newsroom/PressAnnouncement/Ucm333695.htm>.

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